

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/32710

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 48/00: CO7H 21/04

US CL : 514/44: 536/24.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44: 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0003092 A1 (KRISSENSEN et al.) 02 January 2003 (02.01.2003), see entire document.	1-3 and 11-14
X	WO 02/083 184 A2 (DE BIZEMONT et al.) 24 October 2002 (24. 10.2002). see entire document.	1-3 and 11-13

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

13 September 2005 (13.09.2005)

Date of mailing of the international search report

15 NOV 2005

Name and mailing address of the ISA/US

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(d) for the following reasons

- 1 ☐ Claims Nos  
because they relate to subject matter not required to be searched by this Authority, namely
- 2 ☐ Claims Nos  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically
- 3 ☐ Claims Nos  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(d)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows  
Please See Continuation Sheet

- 1 ☐ As all required additional search fees were timely paid by the applicant this international search report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying additional fees this Authority did not invite payment of any additional fees
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant this international search report covers only those claims for which fees were paid specifically claims Nos
- 4 ☒ No required additional search fees were timely paid by the applicant Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos 1-3 and 11-14 (and SEQ ID NO D)

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation

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### BOX III OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

- I Claims 1-3 and 11-14, drawn to a method for inhibiting expression of a hypoxia-inducible gene in a cell, more specifically HIF-1, the method comprising introducing an RNA into the cell in an amount sufficient to inhibit the expression of the hypoxia-inducible gene, wherein the HIF-1 gene comprises a nucleotide sequence of SEQ ID NO 1
- II Claims 1-3 and 11-14 drawn to a method for inhibiting expression of a hypoxia-inducible gene in a cell, more specifically HIF-1, the method comprising introducing an RNA into the cell in an amount sufficient to inhibit the expression of the hypoxia-inducible gene, wherein the HIF-1 gene comprises a nucleotide sequence of SEQ ID NO 3
- III Claims 1 and 4-14 drawn to a method for inhibiting expression of a hypoxia-inducible gene in a cell, the method comprising introducing RNA into the cell in an amount sufficient to inhibit the expression of the hypoxia-inducible gene, wherein the RNA comprises a double stranded region
- IV Claims 15-24 and 27-32, drawn to a method for inhibiting expression of a hypoxia-inducible gene in a subject comprising introducing a siRNA into the target cell of the subject, further comprising contacting the cell with a vector comprising the siRNA
- V Claims 15-34 drawn to a method for inhibiting expression of a hypoxia-inducible gene in a subject comprising introducing an siRNA into the target cell of the subject, further comprising contacting the cell with a vector comprising the siRNA, wherein the gene is HIF-1 comprising the sequence of SEQ ID NO 1
- VI Claims 15-34 drawn to a method for inhibiting expression of a hypoxia-inducible gene in a subject comprising introducing an siRNA into the target cell of the subject, further comprising contacting the cell with a vector comprising the siRNA, wherein the gene is HIF-1 comprising the sequence of SEQ ID NO 3
- VII Claims 36-43 and 45-63, drawn to a small interfering RNA molecule that down regulates expression of a HIF-1 gene by RNA interference, wherein the sense region comprises a contiguous 19-30 nucleotide subsequence of SEQ ID NO 1
- VIII Claims 36-43 and 45-63, drawn to a small interfering RNA molecule that down regulates expression of a HIF-1 gene by RNA interference, wherein the sense region comprises a contiguous 19-30 nucleotide subsequence of SEQ ID NO 3
- IX Claims 36-42 and 44-63, drawn to a small interfering RNA molecule that down regulates expression of a HIF-1 gene by RNA interference, wherein the sense region comprises the sequence of SEQ ID NO 7 and the antisense region comprises a 100% complement of SEQ ID NO 7
- I This international searching authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below

According to the guidelines in Section (f)(1)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a

Markush-group are of similar nature. For chemical alternatives, such as the claimed antisense sequences, the Markush group shall be regarded as being of similar nature when

- (A) all alternatives have a common property or activity and
- (B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or
- (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art-recognized class of compounds in the art to which the invention pertains

The instant antisense sequences are considered to be each separate inventions for the following reasons

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1 The sequences do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. Although the sequence target and modulate expression of the same gene, each sequence behaves  
1 in a different way in the context of the claimed invention. Each sequence targets a different and specific region of the target gene and each sequence modifies (either increases or decreases) the expression of the gene to  
i varying degrees. Each member of the class cannot be substituted, one for the other, with the expectation that  
j the same intended result would be achieved.

1 Further, although the sequence target the same gene, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the specific  
1 sequences is lacking and each sequence claimed is considered to constitute a special technical feature.

Additionally, the special technical feature of claim 1 is drawn to a method of inhibiting expression of a hypoxia-inducible gene in a cell, the method comprising introducing a RNA into the cell in an amount sufficient to inhibit expression of the hypoxia-inducible gene, wherein the RNA comprises a ribonucleotide sequence which corresponds to the coding strand of the hypoxia-inducible gene.

Krissansen et al teach a method of treatment for a mammal comprising the administration to said mammal of an immunotherapeutic agent in conjunction with a tumor growth restricting agent, wherein the tumor growth restricting agent is an antisense HIF-1. Therefore, there is no special technical feature.